REMARKS

Claims 1-54 were submitted with the application as filed. In a concurrently filed preliminary amendment, Applicants canceled claims 1-54 and added new claims 55 and 56. In their Second Preliminary Amendment, filed August 3, 2006, Applicants canceled claims 55 and 56 and added new claims 57-98. In their September 15, 2009 Response to a Restriction Requirement, Applicants elected without traverse Group V (claims 72-85 and 96, drawn to products of formula IV, formula V, formula VI, formula VII, and formula VIIa). Currently, Applicants amend claims 74, 77, and 78, and add new claim 99. Claims 57-99 are pending, and claims 57-71, 86-95, 97, and 98 are withdrawn.

I. CLAIM REJECTIONS UNDER 35 U.S.C. § 112

A. Rejection of Claims 72-85 and 96 Under § 112, First Paragraph

The Office Action rejects claims 72-85 and 96 under 35 U.S.C. § 112, first paragraph:

> …[T]he specification, while being enabling for a salt or N-oxide of the compounds, does not reasonably provide enablement for a solvate of the compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants respectfully traverse this rejection.

According to the Court of Appeals for the Federal Circuit in the case of *In re Wands,*

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "The key word is 'undue,' not 'experimentation.'" The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

In re Wands, 858 F.2d 731, 736 -737 (Fed. Cir. 1988) (citations omitted). Determining whether undue experimentation is required to practice a claimed invention turns on weighing many

factors summarized in *In re Wands*, for example: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.* at 737.

A specification need not contain any example of the invention, as the issue is whether the disclosure enables one skilled in the art to practice the invention without undue experimentation. *In re Borkowski,* 422 F.2d 904, 908 (CCPA 1970). Simply, a determination that undue experimentation is necessary to practice the invention does not necessarily follow from a lack of examples in the specification.

Initially, Applicants note that the present application is directed to the preparation and use of compounds that are active as inhibitors of cyclin dependent kinase, glycogen synthase kinase-3, or Aurora kinase, which are useful in the treatment of disorders such as cancer, in which inhibition of the kinases would be therapeutically useful.

The activity of the compounds of the invention is demonstrated by a wealth of biological data in the patent specification. There are also synthetic examples that provide good experimental support for the scope of the claims, as evidenced, for example, by U.S. Application No. 11/813,031, which published as U.S. 2008-0132495 on June 5, 2008 (cited as reference B9 on Applicants' July 16, 2009 Information Disclosure Statement), and is commonly assigned with the instant application. Example 67B of the '031 application discloses the formation of a dihydrate, 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base dihydrate (termed FB2 in later examples), which falls within the scope of instantly pending independent claim 72. Example 68 of the '031 application describes the characterization of the FB2 dihydrate by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and polarized light microscopy. Example 69 discloses the small molecule crystal structure of FB2, and Example 72 discusses the examination of the stability of the dihydrate via X-ray powder diffraction (XRPD).

The compounds of the invention have been shown to exert their biological effects while in solution. Whether or not the compound is in the form of a crystalline solvate is essentially

immaterial to the biological activity of the compounds. Thus, one skilled in the art would be able to predict the biological properties of the solvate from knowledge of the non-solvate because, once the solvate and non-solvate have passed into solution, they are one and the same.

Indeed, solvates are very well known in pharmaceutical chemistry. They can be important to the processes for the preparation of a substance (e.g., in relation to their purification, the storage of the substance, e.g., its stability, and the ease of handling the substance). In most cases, solvates are formed as part of the isolation or purification stages of a chemical synthesis without any intent on the part of the skilled artisan. In such circumstances, the skilled artisan can determine by means of standard and long-used techniques whether a solvate has formed. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray crystallography (e.g. single crystal X-ray crystallography or X-ray powder diffraction), and solid state NMR (SS-NMR, also known as magic angle spinning NMR or MAS-NMR). Indeed, these were the very techniques that were described in the '031 U.S. patent application for their use in characterizing the formation of the FB2 dihydrate. Such techniques are as much a part of the standard analytical toolkit of the skilled artisan as are NMR, IR, HPLC, and MS.

Alternatively, if the skilled artisan wished to deliberately form a solvate, the general techniques for doing so are part of the general knowledge shared by those in the art. Such techniques would represent a subset of the technique of crystallization or recrystallization, a technique that all organic chemists learn at the very outset of their chemical training, and which is fundamental to their functioning as organic chemists. In order to form solvates, the skilled artisan would be aware that it would be necessary to include in the crystallization conditions an amount of the solvent required for the particular solvate. Thereafter, to establish whether solvates had formed, routine procedures as described above would be utilized without any undue experimentation.

Applicants respectfully submit that a careful analysis of the *In re Wands* factors demonstrates that the present invention does not require undue experimentation for the skilled artisan to make and use the full scope of the claims, such that the claims are enabled.

i. The State of the Prior Art and Predictability in the Art

Turning to the first factor, the Office Action makes the conclusory allegation that "Determining if a particular compound would form a solvate or hydrate would require synthesis and recrystallization of the compound solvate using a variety of solvents, temperatures and humidities. The experimentation for solvates or hydrates is potentially open-ended." Office Action at 5-6.

Applicants reiterate the *In re Wands* precedent, which explicitly establishes that enablement is not precluded by the need for experimentation, but rather, only by *undue* experimentation. As discussed above, solvates are very well known in pharmaceutical chemistry. Given that solvates are well known, the skilled artisan, and in particular the skilled pharmaceutical chemist, would be expected to have knowledge of such forms as a part of his or her common general knowledge. Such common general knowledge would inevitably include knowledge of how to form solvates and how to recognize and characterize solvates when they are formed.

The skilled artisan would therefore readily be able to determine whether or not the isolation conditions or purification conditions used to prepare a given compound had given rise to a solvate. This could be done by standard and long-used methods such as TGA, DSC, and X-ray crystallography, methods which are well known to the skilled person and which are considered routine, **not** undue experimentation. Indeed, the disclosure of the '031 application describes the formation, identification, and characterization of instantly claimed solvates using such methods. As such, the '031 disclosure demonstrates that the instant claim scope is enabled, and it refutes the assertion that experimentation for solvates would be open-ended.

The Office Action additionally states at page 7 that "the formation, composition and therapeutic activity of solvates are unpredictable." Applicants submit that skilled artisans are familiar with common, long-used methods that enable the routine formation and identification of solvates. The appropriate standard to apply in this instance is not whether practicing the invention is free of all unpredictability. Rather, it is accepted that some routine experimentation can be required, provided that such experimentation is not undue.

According to MPEP § 2164.06, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (citing *In re Angstadt,* 537 F.2d 489, 502-04 (CCPA 1976)). Applying a standard that looks for absolute predictability, as suggested in the Office Action, is in direct contradiction to Patent Office policy and case law, as described above. Further, application of such a standard would lead to a failure of that standard by the overwhelming majority of pharmaceutical and other scientific developments.

The data presented in the instant application demonstrate that compounds of the present invention are potent inhibitors of cyclin dependent kinase, glycogen synthase kinase-3, or Aurora kinase. The Office Action provides no basis whatsoever for suggesting that such activity would not also be demonstrated by solvates of the present compounds. On the contrary, the fundamental biological properties of the solvates would be absolutely predictable from the activities of the parent compounds because, once dissolved and in solution, they are effectively one and the same.

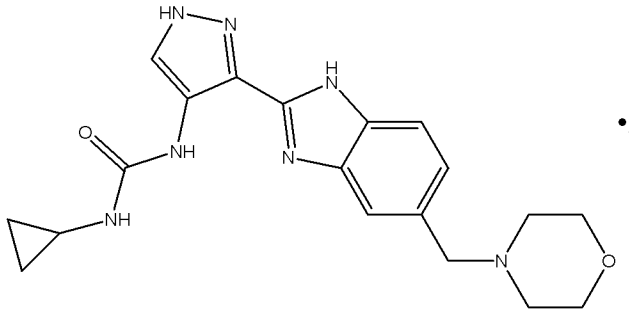
For these reasons, the art is not unpredictable as alleged in the Office Action, and one of skill in the art would only have to engage in a limited amount of routine experimentation to provide solvates according to the present invention.

ii. The Amount of Direction or Guidance and Working Examples

The Office Action indicates that no working examples or guidance are provided in the specification as to preparing any solvate of the claimed compounds: "The specification shows no evidence of the formation and actual existence of solvates and hydrates. Hence, Applicant must show formation of solvates or limit the claims accordingly." Office Action at 6.

Applicants respectively submit that the presence or absence of working examples is not indicative of the enablement of pending claims. Where, as here, the techniques utilized to prepare solvates of the claimed compositions are well known to the skilled artisan, it is not necessary for such basic knowledge present in the art to be repeated in the specification.

Notwithstanding the fact that working examples are not necessary for enablement, Applicants refer the Examiner to U.S. Application No. 11/813,031, which shows the formation of claimed solvates. Applicants' later publication in the '031 application illustrates the ease with which solvates can be obtained and analyzed using standard techniques of the type discussed above. As described above, the '031 application describes and exemplifies a stable hydrate of the formula (1) below.



$\cdot 2H_2O$

(1)

On page 81 of the published application, data are presented relating to the formation of a dihydrate of the free base of the compound of formula (1) using standardized crystallization methods and commonplace solvents. The relevant text is as follows:

Example 67

Synthesis of Crystalline Free Base And Crystalline Salt Forms Of 1-Cyclopropyl-3-[3-(5-Morpholin-4-ylmethyl-1H-Benzoimidazol-2-yl)-1H-Pyrazol-4-yl]-Urea

...

B. Preparation of 1-Cyclopropyl-3-[3-(5-Morpholin-4-ylmethyl-1H-Benzoimidazol-2-yl)-1H-Pyrazol-4-yl]-Urea Free Base Dihydrate

[0912] A sample of crude 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base was dissolved in THF and then concentrated in vacuo to a minimum volume (~4 volumes). To the solution was added water dropwise (2-4 volumes) until the solution became turbid. A small amount of THF was added to re-establish solution clarity and the mixture left to stand overnight to give a crystalline material which was air-dried to give 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base dihydrate.

In examples 68 and 69 on pages 81-84, data are presented relating to the identification and characterization of the dihydrate using standard methods such as TGA, DSC, X-ray crystallography, and SS-NMR. The use of such standard techniques, which are not considered undue experimentations, underscores the enablement of the present invention. The experimental results described in the '031 application illustrate the ease with which solvates can be prepared and characterized. While working examples are *not* necessary to enable claims to solvates as presented in the instant application, the results demonstrate the "**formation and actual existence of solvates**" as the Office Action asserts is required.

iii. Breadth of the Claims

The pending claims include solvates of the claimed compounds. Such breadth of the claims is not overbroad, and is in fact within the scope of the claims recently granted by the U.S. Patent and Trademark Office in similar applications.

Each of U.S. Patent Nos. 7,396,935, 7,405,226, 7,407,989, 7,414,050, 7,417,065, and 7,419,991 have granted within the past two years, with claims that include solvates of the claimed compounds. Further, each of these patents lacks a description of solvates in the specification over and above that which is considered knowledge available in the art at the time of filing, which therefore is not required to be present in the specification.

Thus, Applicants submit that the scope of the claims is in keeping with other recently granted U.S. Patents and is therefore not overbroad.

iv. Quantity of Experimentation Needed and Skill in the Art

In the Office Action, the Examiner asserts that the quantity of experimentation needed is "undue experimentation". As discussed above, the techniques used to prepare solvates comprise basic techniques taught to chemists long before they have acquired the requisite knowledge to be considered one of skill in the art. The skilled artisan requires only routine experimentation to provide solvates and to characterize solvates that are formed. Also, it is noted that *In re Wands* states that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

In re Wands, 858 F.2d 731, 797 (Fed. Cir. 1988) (citing *In re Angstadt,* 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976).

The mere fact that some experimentation is required does not indicate that such experimentation would be undue. Rather, that determination must be made in conjunction with the state and predictability of the art, which as described above, results only in routine experimentation to make and use the present invention. Indeed, the disclosure in the '031 application is precisely on point and provides more than sufficient guidance with respect to making and identifying the claimed solvates. Thus, the skilled artisan would not be required to engage in undue experimentation to arrive at the present invention.

v. The Claims Are Enabled

Accordingly, it is believed that the identification and/or preparation of solvates would not be an undue burden on the skilled artisan and that it is reasonable for a claim to compounds, *per se,* to also cover the solvates of the compounds, especially in view of those recently granted patents provided above which include claims of similar scope without the benefit of significantly different disclosures as to solvates. Indeed, it would be unfair on the Applicants, and a poor reward for their ingenuity in developing the compounds of the invention, if solvates were not explicitly covered by the claims, particularly when such solvates would have substantially the same biological activity *in vivo* as the parent compounds.

For all of the reasons above, Applicants respectfully submit that in light of the information presented in the patent specification and the common general knowledge of the skilled artisan, the instant claims are fully enabled in their scope. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, are therefore respectfully requested.

B. Rejection of Claims 74, 77, and 78 Under § 112, Second Paragraph

The Office Action rejects claims 74, 77, and 78, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Office Action asserts that in claim 74, the terms "R^{1b}-A-NH", "R^{1b}-C(=O)NH" and "R^{1b}-A-NHC(=O)" lack antecedent basis from claim 72. Claim 74 has been amended to exclude these terms. Applicants have added new claim 99, which recites the terms "R^{1b}-A-NH", "R^{1b}-C(=O)NH" and "R^{1b}-A-NHC(=O)", and depends from claim 73, which provides antecedent basis for said terms.

The Office Action asserts that in claim 77, the "R^{1a}" definition lacks antecedent basis from claim 72. Claim 77 has been amended to define R^{1a} as being selected from "unsubstituted three and five membered cycloalkyl groups", which is supported by claim 72.

The Office Action asserts that in claim 78, R^{6a}-R^{9a} representing a C_{1-8} hydrocarbyl group substituted by C_{1-4} acyloxy lacks antecedent basis from claim 72. It is also asserted that under the definition (a) of R^{6a}-R^{9a} in claim 78, the phrase "and R^c, X^1 and X^2" is unclear. Applicants have amended claim 78 to exclude the possibility of any of R^{6a}-R^{9a} representing a C_{1-8} hydrocarbyl group substituted by C_{1-4} acyloxy. The phrase "and R^c, X^1 and X^2" has been deleted from claim 72.

The Office Action also asserts that in claim 78, under the definition (a) of R^{6a}-R^{9a}, the adjacent pair of substituents representing "a non-aromatic five or six membered ring" lacks antecedent basis because the phrase does not stipulate that the ring must be a heterocyclic ring as found in claim 72. The last section of the definition of R^{6a}-R^{9a} recites, in *ipsis verbis* as claim 78, that "an adjacent pair of substituents selected from R^{6a}, R^{7a}, R^{8a} and R^{9a} together with the carbon atoms to which they are attached may form a non-aromatic five or six membered ring containing up to three heteroatoms selected from O, N and S." Applicants respectfully submit that antecedent basis for the rejected claim language is found in claim 72.

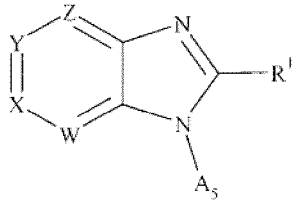
Applicants respectfully assert that the §112, second paragraph rejections of claims 74, 77, and 78 are overcome.

II. CLAIM REJECTIONS FOR NONSTATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

The Office Action indicates that claims 72-85 and 96 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-83, 104, 106-115, and 125-127 of copending Application No. 11/813,031. Applicants will await lifting of the provisional rejection in the instant case until the claims are found allowable.

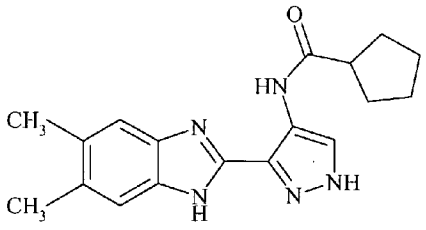
III. CLAIM REJECTIONS UNDER 35 U.S.C. § 103

The Office Action rejects claims 72-85 and 96 under 35 U.S.C. § 103(a) as being obvious in view of Edwards et al. (WO2003/035065). Edwards discloses compounds containing the general structural formula **(1x)**:



(Ix)

The Examiner has drawn particular attention to compound 248(f) on page 421 of WO 2003/035065, cyclopentanecarboxylic acid [3-(5,6-dimethyl-1*H*-benzoimidazol-2-yl)-1*H*-pyrazol-4-yl]-amide, which is outside the scope of Applicants' claims.



248(f)

A. A *Prima Facie Case* of Obviousness in View of Edwards Has Not Been Made Because Edwards' Formula (1x) Is Large in Breadth, the Reference Does not Disclose Any Species Within the Instant Claim Scope, and All Preferred, Optimally Active Embodiments Are Significantly Different in Structure from Applicants' Claimed Compounds.

The Office Action asserts that Applicants' claims 72-85 and 96 are obvious in view of Edwards because the instantly claimed compounds are generically described in the prior art. The Action cites to *In re Lemin* as support for the assertion that "[t]he indiscriminate selection of 'some' among 'many' is *prima facie* obvious," and the Action further alleges that the "motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity." Office Action at 15-16.

In *In re Lemin*, the claimed composition comprised merely a surfactant added to a known compound. The known compound in that case was disclosed in the prior art, and fell within the scope of the claimed compounds. *In re Lemin*, 326 F.2d 437, 438 (CCPA 1964). The instant case is distinguishable from *Lemin* because, as indicated above, the known compounds do not fall within the scope of Applicants' claims. Rather, in the instant case, the cited Edwards compound is *outside* of the subject matter encompassed by the claims.

The only Edwards compound mentioned in the instant Office Action is example 248(f), which is outside of Applicants' claim scope. Otherwise, the Office Action merely asserts that the instantly claimed compounds are generically described in the Edwards reference. As support for this rejection, the Action cites to, for example, pages 4-9 of Edwards, which show formula **(1x)**, *supra.*

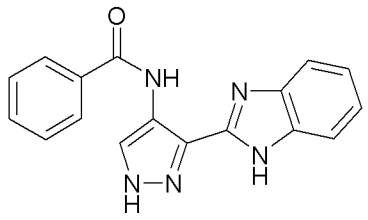
U.S. Patent Application No. 10/279,834 is the corresponding U.S. application to the cited Edwards (WO2003/035065) reference. It appears from the phraseology of the rejection issued in the '834 application, that the Examiner shares Applicants' view that the Edwards formula **(1x)** does not constitute the disclosure of the Edwards application, and that, in fact, the actual disclosure of Edwards is considerably narrower than formula **(1x)**. Indeed, this was recognized by the USPTO in its December 4, 2003 Office Action in the Edwards '834 application, which indicated that formula **(1x)** was so broad that it was impossible to even determine what subject matter was included or excluded. '834 Office Action at 4. As demonstrated by this rejection,

based on the incredibly expansive scope of Edwards' formula **(1x)**, it was clear to the Examiner that the applicants could not have possessed an idea of what they were actually claiming.

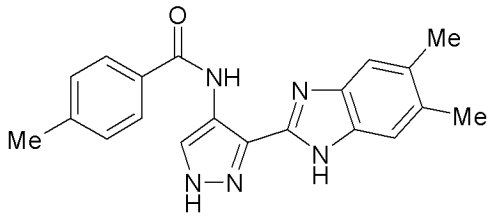
Of the many species disclosed in the Edwards application, none fall within Applicants' claim scope. Moreover, of the hundreds of Edwards compounds, all of the species with the greatest activities (lowest IC_{50} values) have core structures that are 3-(benzoimidazol-2-yl)-indazoles, which are significantly different from the compounds encompassed by the instant Applicants' claims. See Table 6, '834 publication at col. 618-621; WO2003/035065 at 563-570.

In view of the above, a person having ordinary skill in the art would not consider the Edwards reference to teach or suggest the instantly claimed compounds. As MPEP § 2144.08(II) provides, "[t]he fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." The very large size of Edwards' formula **(1x)** genus (*see* MPEP § 2144.08(II)(A)(4)(a)), together with the fact that all of the most active embodiments are different in structure from the claimed genus (*see* MPEP § 2144.08(II)(A)(4)(c)), weigh against a determination of obviousness (*see* id. (citing *Baird,* 16 F.3d at 382-383 (reversing obviousness rejection of species in view of large size of genus and disclosed "optimum" species))). Applicants therefore respectfully assert that the instantly claimed invention is not obvious in view of Edwards, and that a *prima facie* case of obviousness has not been established.

B. Even if a *Prima Facie* Case of Obviousness Were Established, the Instantly Claimed Compounds Are Not Obvious in View of Edwards Because They Have Better Activities than Edwards' Compounds A1-B32 and A9-B101.

The present application contains comparative data comparing compounds A1-B32 and A9-B101 from Edwards (WO 2003/035065) with compounds of the present application. Comparative Example A of the instant application compares the CDK inhibitory activity of an Edwards compound disclosed as combination A1-B32 on page 110, column 2 table 2 of WO2003/035065 (hereinafter Compound A"),  , with compounds of

the instant invention having a similarly unsubstituted benzimidazole group but having substituents on the phenyl ring.

Comparative Example B of the instant application compares the CDK inhibitory activity of an Edwards compound disclosed as combination A9-B101 in column 1 of the table on page 117 of WO2003/035065 (hereinafter "Compound B"), also exemplified as Example (y) on page 428 of WO2003/035065,  , with Applicants' Example 73, which is the 2,6-difluorophenyl analogue of Compound B.

The results of Comparative Tests A and B are set out in Example 309 on pages 260 to 261 of Applicants' specification. As shown below, the CDK inhibitory activities of the instant compounds (determined using the protocol set out Applicants' Example 306 on page 257 of the instant specification) were demonstrated to be significantly better than the activity of Compound A.

COMPARATIVE EXAMPLE A

Compound/ Example No.	**Phenyl ring substitution**	**IC_{50} (μM) or % inhibition**
Compound A	unsubstituted	0.0967 μM
Example 6	2,6-difluorophenyl	0.0048 μM
Example 43	2-chloro-6-fluorophenyl	52%@ 0.003 μM
Example 44	2-fluoro-6-methoxyphenyl	57%@ 0.003 μM
Example 56	2,4,6-trifluorophenyl	58%@0.003 μM

Example 57	2-chloro-6-methylphenyl	41%@0.003 μM
Example 59	2,6-dichlorophenyl	67%@0.003 μM

Similarly, Compound B was found to have an IC_{50} value of 3μM in the CDK inhibitory assay described in Example 306, while Applicants' Example 73 compound was found to have an IC_{50} value of 0.0046 μM.

Applicants' specification also contains comparative data relating to the anti-proliferative activity of the compounds of the instant invention, which was determined by measuring inhibition of cell growth in the HCT-116 cell line. The results indicate that Example 73 has an IC_{50} value of 0.49 μM in HCT-116 cell line (determined using the protocol set out in Applicants' Example 310), compared with Compound B, which has an IC_{50} value of 5.7 μM in HCT-116 cell line.

The above comparative data demonstrate that compounds of the present invention have substantially better activities than compounds of WO2003/035065 in both kinase assays and cell proliferation assays. Such advantages could not have been predicted from the Edwards application.

Applicants respectfully submit that even if a *prima facie* case of obviousness were established, the above data rebut that presumption by demonstrating the unexpected advantage of the instantly claimed compounds over Edwards. As such, the instantly claimed compounds are not obvious in view of Edwards.

Further, the present compounds are directed against entirely different protein kinases from the Edwards compounds. Indeed, one of the advantages of the present invention is the provision of compounds having activity against CDK, GSK-3 and/or Aurora kinases. All three types of kinase are part of the family of **serine/threonine kinases**, as is explained in the introductory paragraphs of the present application. Both CDK and Aurora kinases are included in cell cycle control. By inhibiting these kinases cell division and proliferation is inhibited or prevented.

By contrast, the compounds of WO 03/035065 are directed to the inhibition of the kinases EGFR, Fak, FLK-1, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Flt-1, IGF-R1, KDR, PDGFR, tie2, VEGFR, ITK and STK. These are all **protein-tyrosine kinases,** a different family of kinases from the kinases against which the present compounds are directed. Page 1, lines 9 to 18 of the present application provides a discussion of the differences between the various types of kinases. The kinases to which the compounds of WO 03/035605 directed have quite different biological properties from the kinases against which the present compounds are targeted.

Furthermore, KDR kinase, the key kinase for which data is provided in WO 03/035065, is implicated in tumour angiogenesis, i.e. the development of blood vessels in tumours whereas the CDK and Aurora kinases targeted by the present compounds are involved in control of the cell cycle. KDR is an angiogenesis target and KDR inhibitors exert an anticancer effect by inhibiting the growth of cancer through the reduction of vasculature development. Aurora and CDK are cell cycle proteins and inhibitors of these kinases elicit their anti-cancer effect by interfering with the cell cycle in cancerous cells and thereby exert a direct action on the tumours. In view of these very substantial differences between the biological modes of action of CDK/Aurora inhibitors and KDR inhibitors, the two would be expected to affect a different range of cancers.

The Syk (spleen tyrosine kinase) is involved in development of the immune response (see page 3, third paragraph of WO 03/035065), whereas the ITK kinase in implicated in the progression of asthma.

Given that the compounds of the present invention are directed against entirely different kinases (protein tyrosine kinases) from the compounds of WO 03/035065, it is submitted that it would not have been in any way predictable that compounds of the present invention would have such good activity against the serine threonine kinases CDK, GSK and/or Aurora kinases. In other words, the activity of the present compounds was not at all obvious from WO 03/035065, which discloses compounds with different activities, and, with regard to the preferred compounds, different structures (3-(benzoimidazol-2-yl)-indazoles) from the instant compounds.

IV. MISCELLANEOUS

No additional fees are believed due. However, the Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment to Deposit Account No. 08-1935, Reference No. 3073.004A.

There being no other outstanding issues, it is believed that the application is in condition for allowance, and such action is respectfully requested.

Respectfully submitted,

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Dated: March 25, 2010

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